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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
HUYNH, PHUONG N	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 03/30/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/000,439	SAXON, ANDREW	
	Examiner	Art Unit	
	Phuong Huynh	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *Three* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 December 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4-5, 9-14,16-34 and 40-49* is/are pending in the application.

4a) Of the above claim(s) *45-49* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4,5,9-14,16-34 and 40-44* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *20 December 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1)☒ Notice of References Cited (PTO-892)

2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

3)☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.

4)☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .

5)☐ Notice of Informal Patent Application (PTO-152)

6)☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 12/20/05 has been entered.

2. Claims 1, 4-5, 9-14, 16-34, and 40-49 are pending.

3. Claims 45-49 stand withdrawn from further consideration by the examiner, 37 C.F.R. 1.142(b) as being drawn to non-elected inventions.

4. Claims 1, 4-5, 9-14, 16-34 and 40-44, drawn to an isolated fusion molecule wherein the autoantigen is myelin basic protein, and a pharmaceutical composition comprising said fusion molecule are being acted upon in this Office Action.

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1, 4-5, 9-14, 16-34 and 40-44 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling only for (1) an isolated fusion molecule comprising hinge-CH2-CH3 of human IgG1 constant region consisting of SEQ ID NO: 2 encoded by SEQ NO: 1 capable of binding to a native IgG inhibitory receptor directly fused to a full length myelin basic protein comprising SEQ ID NO: 12 or a myelin basic protein epitope consisting of the amino acid sequence of SEQ ID NO: 13 wherein the fusion molecule is capable of specific binding to a native IgE receptor through a myelin protein specific IgE antibody, (2) the said fusion protein wherein the native IgG inhibitory receptor is a low-affinity FcγRIIb IgG receptor, (3) the said fusion protein wherein said IgE receptor is a high-affinity FcεRI IgE receptor or a low-affinity FcεRII IgE receptor, **does not** reasonably provide enablement for any fusion molecule as set forth in claims 1, 4-5, 9-14, 16-34 and 40-44 for treatment or "prevention" of any autoimmune disease.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in **scope** with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

The claims are drawn to any isolate fusion molecule comprising any first polypeptide comprising at least 85% identity to any IgG heavy chain constant region connected directly or indirectly via a polypeptide linker to any second polypeptide autoantigen sequence which comprises at least 90% sequence identity to any "portion" of the amino acid sequence of myelin basic protein (MBP) that are capable of cross-linking any native IgG inhibitory receptor and any native IgE receptor through myelin specific autoantibody IgE for treating and preventing any immune disease, any immune disease such as any autoimmune disease.

The term "portion" as defined in the specification at page 29 is any portion of a polypeptide may range in size from two amino acid residues to the entire amino acid sequence minus one amino acid. The term "at least a portion" encompasses portions as well as the whole of the composition of matter.

The term "high stringent conditions" as defined in the specification at page 24 "*may be* hybridization in 50% formamide, 6x SSC (0.75 M NaC1, 0.075 M sodium citrate), 50 mM sodium phosphate (PH 6.8), 0.1% sodium pyrophosphate, 5 x Denhardt's solution, sonicated salmon sperm DNA (100 μg/ml, 0.5% SDS, and 10% dextran sulfate at 42°C, with washes at 42°C in 2x SSC (sodium chloride/sodium citrate) and 0.1% SDS at 55OC, followed by a high-stringency wash consisting of 0.2x SSC containing 0.1% SDS at 42°C.

The term "IgG inhibitory receptor" as defined in the specification at page 19 is any member of inhibitory receptor superfamily (IRS), now known or hereafter discover, that is capable of attenuating an FcER-mediated response, regardless of whether it is mediated via IgE

acting through a high-affinity IgE receptor, e.g. FcERI, or a low-affinity IgE receptor, or by another mechanism such as an autoantibody to the FcER.

The specification does not teach how to identify other portion ranging from two amino acids to of myelin basic protein that has at least 10% amino acids difference in the claimed fusion protein that retains the activity for the intended use such as treating and preventing autoimmune disease. There is not a single fragment from the smallest to the largest fragment of myelin basic protein fused to any IgG heavy chain constant region shows any biological effect for treating immune disease, any immune disease such as autoimmune disease.

The specification discloses only an isolated fusion molecule comprising a first polypeptide wherein the first polypeptide consisting of a hinge-CH2-CH3 of human IgG1 constant region of SEQ ID NO: 2 encoded by SEQ ID NO: 1 fused to a full length myelin basic protein comprising SEQ ID NO: 12 or a myelin basic protein epitope consisting the amino acid sequence of SEQ ID NO: 13, and (2) an isolated fusion molecule the hinge-CH2-CH3 of human IgG1 constant region consisting of SEQ ID NO: 1 fused to a human IgE constant region CH2-CH3-CH4 domains of SEQID NO: 7 for inhibiting IgE mediated release of histamine.

The specification does not teach how to make and use all fusion molecule mentioned above for treating, much less for "preventing" any autoimmune disease because of the following reasons. First, the structure such as the amino acid sequence of the fusion molecule is required. Second, there is insufficient guidance as to the structure and the length of the first polypeptide within the fusion protein without the amino acid sequence. The specification does not teach which amino acids within the full-length sequence of all IgG heavy chain constant region are critical and can or cannot be change such as substitution, deletion, addition and combination thereof and whether the resulting IgG heavy chain constant region merely have 85% sequence identity with an IgG heavy chain constant region still binds to which native IgG inhibitory receptor. Further, the term "comprising" is open-ended. It expands the first polypeptide to infinity, such as the full-length sequence of IgG, not just the Fc fragment. In addition to the problem mentioned above, the term "at least 85% identity" means there is at least 15% difference. Without knowing the length of the first polypeptide, it is not clear how one skill in the art to come up with the sequence identity that based on the total number of amino acids in the first polypeptide. Even if the length of the sequence is recited in the claim, there is insufficient guidance as to which amino acids within the IgG heavy chain constant region to be substituted, deleted, added and/or combination thereof such that the resulting IgG heavy chain constant region

still binds to which native IgG inhibitory receptor. It is known in the art that even a single amino acid change in a protein leads to unpredictable changes in the biological activity of the protein.

Stryer *et al*, of record, teach that a protein is highly dependent on the overall structure of the protein itself and that the primary amino acid sequence determines the conformational of the protein (See enclosed appropriate pages).

Ngo *et al*, of record, teach that the amino acid positions within the polypeptide/protein that can tolerate change such as conservative substitution or no substitution, addition or deletion which are critical to maintain the protein's structure/function will require guidance (See Ngo et al., 1994, The Protein Folding Problem and Tertiary Structure Prediction, pp. 492-495).

Tao et al teach the ability to activate complement and to bind to FcγRI, both of which are dependent on the CH2 domain of IgG heavy chain (see entire document, page 2599, col. 2, second full paragraph, in particular). Tao et al teach even a single amino acid substitution in the CH2 domain of human IgGs from Asn-297 to His for IgG1 or Lys for IgG3 affected the structure and functional properties of the human IgGs. The resulting aglycosylated IgGs lose the ability to activate complement (C) (see page 2598, Fig 2, page 2599, col. 2, third paragraph, in particular), lost the ability to bind FcγRI (see page 2600, col. 1, first paragraph, in particular) and shortening the serum half-life of the aglycosylated IgG3 (see abstract, in particular).

Third, with regard to the second polypeptide autoantigen in the fusion protein, there is insufficient guidance as to the structure and length of the second polypeptide autoantigen within the fusion protein without the amino acid sequence. Specifically, there is insufficient guidance as to which "portion" of the myelin basic protein in the second polypeptide autoantigen is part of the fusion molecule. Given the "portion" of autoantigen sequence can be any length, it is not clear how one skill in the art be able to determine the sequence identity given the length is not finite. It is known in the art that even a single amino acid change in a protein leads to unpredictable changes in the biological activity of the protein.

McDevitt et al teach administering autoantigen comprising a "portion" of an autoantigen such as epitopes 206-220, 221-235 and 286-300 of GAD to NOD mice resulted in the prompt onset of an immediate hypersensitivity and death of animal (page 14628, col. 2, last paragraph, in particular). Without guidance as to the portion or epitope of autoantigen to be fused to the any IgG heavy chain constant region, it is unpredictable which fusion molecule is effective for treating any autoimmune disease, much less for "preventing" all autoimmune diseases (claim 44).

Forth, with regard to percentage of sequence identity (claims 1 and 18-21), in addition to the lack sequence for the first and second polypeptides in the fusion molecule mentioned above, there is insufficient guidance as to which amino acids within the full-length polypeptide can be modified and yet maintain its function. It is known in the art that the relationship between the amino acid sequence of a protein (polypeptide) and its tertiary structure (i.e. its binding activity) are not well understood and are not predictable (see Ngo et al., in The Protein Folding Problem and Tertiary Structure Prediction, 1994, Merz, et al., (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495). There is no recognition in the art that sequence with identity predicts biological function. It is known in the art that even a single amino acid changes or differences in a protein's amino acid sequence can have dramatic effects on the protein's function. Mikayama *et al*, of record, teach that the human glycosylation-inhibiting factor (GIF) protein differs from human macrophage migration inhibitory factor (MIF) by a single amino acid residue (Figure 1 in particular). Yet, Mikayama *et al.* further teach that GIF is unable to carry out the function of MIF and MIF does not demonstrate GIF bioactivity (Abstract in particular). It is also known in the art that amino acid sequence determines the function of the polypeptide or protein. However, the predictability of which changes can be tolerated in an amino acid sequence and still retain similar functions and properties requires a knowledge of, and guidance such as which amino acids within the full-length polypeptide are tolerant of modification and which amino acid residues are conserved or less tolerant to modification in which the product's structure relates to its functional usefulness. The use of "percent" in conjunction with any of the various terms that refer to sequence identity or similarity is a problem because sequence identity between two sequences has no common meaning within the art. The term "percent" is relative and can be defined by the algorithm and parameter values set when using the algorithm used to compare the sequences. The scoring of gaps when comparing one sequence to another introduces uncertainty as to the percent of similarity between two sequences. Because applicants have not disclosed the specific condition used to score sequence identity while using any computer program, it is unpredictable to determine which amino acid sequences of autoantigen in the claimed fusion molecule will have at least about 90% identity to which "portion" of myelin basic protein fused to which first polypeptide will have at least 85% sequence identity to which IgG heavy chain is effective for treating multiple sclerosis. Even if the autoantigen is "comprises at the amino acid sequence of SEQ ID NO: 13 (claim 10), SEQ ID NO: 13 is an epitope or fragment of myelin basic protein.

Further, the term "comprises" expands the fragment to include additional amino acids at either or both ends of SEQ ID NO: 3. There is insufficient guidance as to which amino acids to be added.

Warrant et al (abstract) teach administering myelin basic protein fragment such as MBP35-58 to multiple sclerosis patient had to effect on the anti-MBP level. However, only administering MBP 75-95 resulted in a significant in the autoantibodies over a period of one month (see abstract, in particular). The specification as filed does not teach which amino acids to be added and whether any fragment of myelin basic protein when fused to any first polypeptide comprising at least 85% identity is effective for treating autoimmune multiple sclerosis. Likewise, the same reasons apply to claims 18-21.

Attwood *et al.* teach that protein function is context-dependent and the state of the art of making functional assignments merely on the basis of some degree of similarity between sequences and the current structure prediction methods is unreliable (See figure, entire document).

Fifth, with regard to claims 24, the term "comprises" is open-ended. It extends the hinge, CH2 and CH3 domains of a native human IgG1 heavy chain constant region to include the light chain such as Fab fragment of the full-length human antibody.

Sixth, with regard to the first polypeptide sequence "comprises an amino acid sequence" encoded by any nucleic acid hybridizing under stringent conditions to which "portion" of the complement of the IgG heavy chain constant region nucleotide of SEQ ID NO: 1 (claim 25), the nucleic acid that hybridizes to the complement of SEQ ID NO: 1 could be an oligonucleotide, which does not encodes the whole IgG heavy chain constant region, let alone binding to a native IgG inhibitory receptor. There is insufficient guidance as to the structure of the oligonucleotide that encodes which portion of the complement of IgG heavy chain constant region that binds native IgG native receptor in the claimed fusion molecule. Further, there is insufficient guidance as to the "hybridization stringent conditions". Further, there is insufficient guidance as to which "portion" of the complement of the IgG heavy chain that the nucleic acid hybridize to. The state of the prior art as exemplified by Wallace *et al,* of record, is such that determining the specificity of the oligo and hybridization conditions are empirical by nature and the effect of mismatches within an oligonucleotide probe is unpredictable. The claim as written is improper for an isolated fusion molecule.

Skolnick *et al*, PTO 1449, teach that sequence-based methods for function prediction are inadequate and knowing a protein's structure does not tell one its function (See abstract, in particular).

Given the unlimited number of undisclosed fusion molecules, there is insufficient in vivo working example demonstrating that any fusion molecules are effective for treating all autoimmune diseases. It has been well known to those skilled in the art at the time the invention was made that minor structural differences among structurally related compounds or compositions could result in substantially different biological or pharmacological activities. Even if the fusion molecule is limited to human Fc fused to the myelin basic protein, there is a lack of in vivo working example demonstrating that the fusion is effective for treating multiple sclerosis, let alone for "the prevention of any immune disease" or autoimmune diseases.

Seventh, with regard to pharmaceutical composition (claims 40-41) and article of manufacture (claims 42-44) comprising any fusion molecule mentioned above for the "treatment" or "prevention" of any immune disease, any immune disease such as any autoimmune disease, given the structure of the fusion molecule is not enable, it follows that any pharmaceutical composition or any article of manufacture comprising the undisclosed fusion molecule are not enabled. Further, a pharmaceutical composition in the absence of in vivo is unpredictable for the following reasons: (1) the fusion molecule may be inactivated before producing an effect, i.e. such as proteolytic degradation, immunological inactivation or due to an inherently short half-life of the protein; (2) the fusion molecule may not reach the target area because, i.e. the protein may not be able to cross the mucosa or the protein may be adsorbed by fluids, cells and tissues where the protein has no effect; and (3) other functional properties, known or unknown, may make the fusion molecule unsuitable for in vivo therapeutic use, i.e. such as adverse side effects prohibitive to the use of such treatment. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

Blanas *et al* (of record, Science 274: 1707-1709, Dec 1996; PTO 1449) teach treating autoimmune rheumatoid arthritis and multiple sclerosis by oral administering autoantigen could lead to onset of autoimmune diabetes (see abstract, in particular).

Couzin *et al*, of record, teach that finding the tell tale antibodies doesn't guarantee that autoimmune diabetes sill strike (See page 1863, Science 300: 1862-65, 2003). Couzin *et al* teach that three major prevention trials have failed to stop autoimmune disorder such as type I diabetes (See entire document).

Mackay *et al,* PTO 1449, teach that two recent phase I clinical trial for treatment of multiple sclerosis by administering myelin basic protein peptide resulted in exacerbations of multiple sclerosis (See page 346, col. 2, in particular). In the absence of guidance and vivo working example, it is unpredictable which pharmaceutical composition comprising the undisclosed fusion molecule is useful for treating multiple sclerosis, let alone for "preventing" any autoimmune disease. The specification does not teach any assays that is useful for screening variants and is predictive of success in vivo. Given the unlimited number of fusion molecule, it is unpredictable which undisclosed fusion protein is effective for treating for treating any immune disease, any autoimmune disease such as multiple sclerosis, let alone "preventing" any immune disease, any immune disease such as any autoimmune disease in the absence of working example (claim 44).

Since the structures of the first and second polypeptides of the claimed fusion molecule mentioned above are not enabled, it follows that any first polypeptide and any second polypeptide connected through any linker (claim 26), any linker such as polypeptide linker (claims 27-28) are not enabled. It also follows that any undisclosed fusion protein comprising at least one amino terminal ubiquination target motif (claim 29), any proteosome proteolysis signal (claims 30-31) or any endopeptidase recognition motif (claims 32-34) are not enabled.

For these reasons, it would require undue experimentation of one skilled in the art to practice the claimed invention. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

In re wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the decision of the court indicates that the more unpredictable the area is, the more specific enablement is necessary. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take an undue amount of experimentation for one skilled in the art to practice the claimed invention.

Applicants' arguments filed 12/20/05 have been fully considered but are not found persuasive.

Applicants' position is that the present invention concerns certain novel fusion molecules that are capable of cross-linking a native IgG inhibitory receptor with a native IgE receptor. The fusion molecules comprise a sequence comprising at least 85% identity to IgG heavy chain sequence linked to a polypeptide autoantigen sequence which comprises at least 90% identity to

myelin basic protein and is capable of being specifically bound by an immunoglobin specific for myelin basic protein. The purpose of these molecules is to allow the myelin basic peptide to function as an immunogen while any fusion peptides that reacted with IgE loaded mast cells would not trigger an adverse reaction. At pages 9-11 of the amendment, applicants summarized the rejection of record. applicants argue that there was a lot of information known in the art about the interaction of IgG inhibitory receptors and IgE receptors. Although unpredictability in the field of recombinant DNA technology is generally view as high, the unpredictability in the particular field to which the present invention pertains is of lesser degree.

In response, the claims are drawn to any isolate fusion molecule comprising any first polypeptide comprising at least 85% identity to any IgG heavy chain constant region connected directly or indirectly via a polypeptide linker to any second polypeptide autoantigen sequence which comprises at least 90% sequence identity to any "portion" of the amino acid sequence of myelin basic protein (MBP) that are capable of cross-linking any native IgG inhibitory receptor and any native IgE receptor through myelin specific autoantibody IgE for treating and preventing any immune disease, any immune disease such as any autoimmune disease. There is insufficient guidance as to the structure of the first and second polypeptide in the claimed fusion protein without the amino acid sequence. There is insufficient guidance as to the structure of the autoantigen sequence that comprises at least 10% difference to at least which portion of the amino acid sequence of myelin basic protein fused to a first polypeptide having at least 15% sequence difference to IgG heavy chain constant region. There is a lack of in vivo working example demonstrating the claimed fusion protein could treat, much less prevent any immune disease such as autoimmune disease involved myelin.

At page 12 of the amendment, applicants argue that the specification teaches which amino acids are necessary for IgG receptor binding (see page 35, lines 1-25) as well as methods to determine the affinity of an Fc domain for its cognate receptor (see, for example, page 55, lines 15-25). The use of the term "comprising" does not result in an infinite number of fusion molecule with unpredictable activities as the Examiner contends.

In response, the term "IgG inhibitory receptor" as defined in the specification at page 19 is any member of inhibitory receptor superfamily (IRS), now known or *hereafter discover*, that is capable of attenuating an FcER-mediated response, regardless of whether it is mediated via IgE acting through a high-affinity IgE receptor, e.g. FcERI, or a low-affinity IgE receptor, or by

another mechanism such as an autoantibody to the FcER. The specification at page 35 discloses only IgG CH2-CH3 domain contains the binding sites for the now known low affinity FcγRIIb, and the CH3 domain of the IgE heavy chain for binding to native IgE FcεRI or IgE FcεRII. The claim does not recite the specific amino acids necessary for IgG receptor binding. The specification does not teach which first polypeptide sequence comprising at least 15% difference with any IgG heavy chain constant region in the fusion protein is capable of specifically binding to which native IgG inhibitory receptor(s). As evidence by the teachings of Tao et al who teach that even a single amino acid substitution in the CH2 domain of human IgGs from Asn-297 to His for IgG1 or Lys for IgG3 affected the structure and functional properties of the human IgGs. The aglycosylated IgGs lose the ability to activate complement (C) (see page 2598, Fig 2, page 2599, col. 2, third paragraph, in particular), lost the ability to bind FcγRI (see page 2600, col. 1, first paragraph, in particular) and shortening the serum half-life of the aglycosylated IgG3 (see abstract, in particular). As to the argument of "comprising", the term "comprising" expands the IgG heavy chain constant fragment to include the Fab portion of the IgG. Further, the term "comprising" expands the "portion" of the myelin basic protein in the fusion molecule to include additional amino acids at either or both ends. There is a lack of guidance as to which amino acids to be added and whether it retains its structure and biological activity, in turn, useful for treating and preventing any autoimmune disease.

At page 13 of the amendment, applicants maintain that the one of skill in the art would know which portion of the second polypeptide was required for binding to the third polypeptide which would bind to the IgE receptor. The specification identifies the epitope necessary for binding with the autoantibody as MBP83-99. Examiner references Warren et al., (1995 abstract) as teaching that the administration of MBP 75-95 resulted in significant autoantibodies, but the administration of MBP35-58 did not affect the anti-MBP level. Accordingly, one of ordinary skill in the art would certainly know which portion of the MBP protein is specifically bound by autoantibodies.

In response, none of the claims recite the specific portion of myelin basic protein such as MBP 83-99 that binds to autoantibodies when administered to the subject in the claimed fusion molecule. The specification does not teach which amino acids within the full-length sequence of myelin basic protein (MBP) are critical and whether the resulting second polypeptide autoantigen sequence comprising at least 10% difference to which "portion" of the myelin basic protein still

capable of specific binding to which native IgE receptors through which third polypeptide sequence. Given the "portion" of autoantigen sequence can be any length, it is not clear how one skill in the art be able to determine the sequence identity given the length is not finite. It is known in the art that even a single amino acid change in a protein leads to unpredictable changes in the biological activity of the protein. Given the intended use of the fusion molecule is for treatment any immune disease or for "prevention" of any immune disease such as any autoimmune disease, as evidence by the teachings of McDevitt et al, administering autoantigen comprising a "portion" of an autoantigen such as epitopes 206-220, 221-235 and 286-300 of GAD to NOD mice resulted in the prompt onset of an immediate hypersensitivity and *death* of animal (page 14628, col. 2, last paragraph, in particular).

Blanas *et al* (of record, Science 274: 1707-1709, Dec 1996; PTO 1449) teach treating autoimmune rheumatoid arthritis and multiple sclerosis by oral administering autoantigen could lead to onset of autoimmune diabetes (see abstract, in particular).

Couzin *et al*, of record, teach that finding the tell tale antibodies doesn't guarantee that autoimmune diabetes sill strike (See page 1863, Science 300: 1862-65, 2003). Couzin *et al* teach that three major prevention trials have failed to stop autoimmune disorder such as type I diabetes (See entire document).

Mackay *et al,* PTO 1449, teach that two recent phase I clinical trial for treatment of multiple sclerosis by administering myelin basic protein peptide resulted in exacerbations of multiple sclerosis (See page 346, col. 2, in particular). It is not clear the reliance of a pharmaceutical composition comprising a fusion molecule comprising any IgG heavy chain constant region fused to any sequence at least 90% sequence identity to any portion of the amino acid sequence of myelin basic protein is appropriate for treating all autoimmune diseases, let alone for "prevention" of any immune diseases in the absence of in vivo working example.

As such, treatment and/or prevention of any immune disease, any immune disease such as any autoimmune disease using any pharmaceutical composition comprising any fusion molecule is highly unpredictable, varies depending on the animal model, means of administration and composition of the fusion molecule.

At pages 13-15 of the amendment, applicants note that the term "IgG heavy chain constant region" is defined in the specification at pages 26 and 36. It does not include the Fab region. Accordingly the term "comprising 85% of the IgG heavy chain constant region" means

that the first polypeptide must exhibit at least 85% identity with the IgG heavy chain constant region. There may of course be additional amino acid residues included in the fusion peptide. However, one of ordinary skill in the art would know whether the fusion molecule contained an amino acid sequence with 85% identity to the IgG heavy chain constant region. Applicant points out that the specification describes methods for the determination of percent identity between two amino acid sequences (see Specification, page 23, lines 4- 13). In fact, the specification teaches specific parameters to be associated with the term "percent identity" as applied to the present invention. Also, one of ordinary skill in the art will recognize that the prior art provides numerous sources that describe IgG Fc sequences highly homologous to the Fc sequences of SEQ ID NO: 3 (see, the Specification at page 26, line 19 - page 27, line 6).

In response, the specification at page 36 discloses "the first polypeptide sequence present in the fusion molecules of the invention has at least about 80%, more preferably at least about 85%, even more preferably at least about 90%, yet more preferably at least about 95%, most preferably at least about 99% sequence identity with the amino acid sequence of the hinge-CH2-CH3 region of a native IgG, e.g. IgG1 immunoglobulin, preferably native human IgG1. In a particularly preferred embodiment, the sequence identity is defined with reference to the human hinge-CH2-CH3 sequence of SEQ ID N0: 3. However, Claim 1 recites an isolated fusion molecule comprising any first polypeptide sequence comprising at least 85% identity with any IgG heavy chain constant region capable of specific binding to any native IgG inhibitory receptor, directly functionally connected to a second polypeptide autoantigen sequence comprising at least 90% sequence identity to at least a portion of the amino acid sequence of myelin basic protein (MBP) and capable of specific binding, through a third polypeptide sequence specific for myelin basic protein, to a native IgE receptor. The first polypeptide is the fusion molecule comprising any sequence at least 85% to any IgG heavy chain constant region capable of binding to any IgG inhibitory receptor. The term "comprising" expands the to the hinge-CH2-CH3 sequence to include the CH1 domain, for example. There is not a single fusion molecule in the specification as filed comprises a first polypeptide sequence comprising any IgG heavy chain constant region such as hinge-CH1-CH2-CH3 fused to myelin basic protein or a fragment thereof.

At pages 16-17 of the amendment, applicants state that Applicant has described a chimeric protein comprising two known sequences with known function. The present application describes, by way of example, additional non-essential but advantageous amino acid sequences

and other elements that find use with the first and second polypeptides of the fusion molecules of the invention. For example, the first and second polypeptide sequences of the fusion molecule can be joined using various linkers (such as those described in the Specification at page 56, lines 4-16). Also, the fusion molecules may contain posttranslational modifications, either naturally occurring or artificial, for example, acetylation, glycosylation and prenylation (see Specification page 21, lines 4 - 24). The Specification teaches that fusion polypeptide variants can be constructed that contain advantageous in selections of various amino acid sequences (page 21, line 25 to page 23, line 3), resulting in fusion molecules that have improved affinity for their respective IgG or IgE Fc receptors (Specification, page 34, line 24 to page 35, line 25). The fusion molecules of the invention can also comprise multiple copies of the IgG and autoantigens, as described in page 54, lines 18-21. Fusion polypeptides further comprising signal sequences for intracellular localization or extracellular export (page 63, lines 20-22), and peptide sequence tags to facilitate fusion molecule purification (page 63, line 32 to page 64, line 3) also find use with the fusion' molecules of the invention.

In response, the issue here is whether the structures of first and second polypeptides within the fusion molecule are enabled. The second "comprising" in claim 1 raises the issue of enablement. This is because the term "comprising" expands the IgG heavy chain constant region to include additional amino acids at either or both ends. The specification discloses only human IgG1 constant region consisting of hinge-CH2-CH3 of IgG heavy constant region of SEQ ID NO: 2. With regard to the autoantigen polypeptide comprising at least 90% sequence identity to at least a portion of the amino acid sequence of myelin basic protein, the term "portion" as defined in the specification at page 29 is any portion of a polypeptide may range in size from *two* amino acid residues to the entire amino acid sequence minus one amino acid. The term "at least a portion" encompasses portions as well as the whole of the composition of matter. There is insufficient guidance as to which "portion" of myelin basic protein is part of the fusion protein, let alone the sequence has at least 90% identity to the undisclosed portion. Amending claim 1 to recite an isolated fusion comprising a first polypeptide sequence "consisting of the hinge-CH2-CH3 of IgG heavy constant region of SEQ ID NO: 2 capable of specific binding to a native IgG inhibitory receptor, directly functionally connected to a second autoantigen polypeptide of myelin basic protein (MBP) or a fragment thereof wherein the fragment consisting of the amino acid sequence of SEQ ID NO: 13 would obviate the issues mentioned above. The term "comprising" immediate after fusion molecule allows that fusion molecule to include linker, posttranslational

modifications, either naturally occurring or artificial, for example, acetylation, glycosylation and prenylation, or signal sequences for intracellular localization or extracellular export.

At pages 18-20 of amendment, applicants summarize the references cited by the Examiner. Applicant presumes that the Examiner intended to cite Davidson et a1., (2001) New England J. of Med. 34545) 340-350, Eds. MacKay & Rosen rather than MacKay et al. Applicants conclude that the legal standard with respect to in vitro or animal be acceptable as a basis for enablement. Blanas indicates that oral administration of ovalbumin autoantigen in mice was found to induce a cytotoxic T lymphocyte response that could lead to the onset of autoimmune diabetes. Blanas does not discuss the MBP peptide or multiple sclerosis. Couzin et al. (2003) is an article reviewing various clinical tests for the treatment and prevention of type I diabetes. Couzin does not discuss the MBP peptide, use of a fusion polypeptide or multiple sclerosis. For the reasons set forth for Blanas, the findings of Couzin et al. cannot be applied properly to the currently claimed invention. Mackay et al, states that two recent phase l clinical trials for treatment of multiple sclerosis by administering altered peptide ligands derived from MBP resulted in either hypersensitivity reactions or exacerbations of multiple sclerosis. (page 346). First, MacKay does not indicate that the altered peptide ligands derived from MBP are functionally attached to the IgG heavy chain constant regions. The purpose of the IgG Fc regions is to prevent the hypersensitivity reaction seen with the peptides as taught by MacKay. Accordingly, MacKay does not teach that the claimed invention will not work. Mackay et al, states that two recent phase I clinical trials for treatment of multiple sclerosis by administering altered peptide ligands derived from MBP resulted in either hypersensitivity reactions or exacerbations of multiple sclerosis. (page 346). First, MacKay does not indicate that the altered peptide ligands derived from MBP are functionally attached to the IgG heavy chain constant regions. The purpose of the IgG Fc regions is to prevent the hypersensitivity reaction seen with the peptides as taught by MacKay. McDevitt, allegedly indicates that administration of GAD autoantigen epitopes in NOD mice was found to induce immediate hypersensitivity that could lead to death. Applicant's fusion molecules comprise the heavy chain constant region of the IgG fused to the MBP peptide. The fusion molecule acts to inhibit the auto allergic reaction. McDevitt does not discuss the administration of a fusion molecule, let alone a fusion molecule comprising an autoantigen fused to the IgG heavy chain constant region, as claimed. Indeed, use of an autoantigen fused to the IgG heavy chain constant region as proposed by Applicant would

be the way to resolve the problem discussed by McDevitt. Applicant previously enclosed later published papers which show that fusion molecules comprising an IgG constant region linked to an IgE constant region successfully reduces histamine release in animals. Clearly such compounds are not inactivated as suggested by the Examiner. Clearly these types of fusion molecules can be successfully administered to animals. Furthermore, the appearance of IgG or other antibodies against the MBP portion of the fusion molecule would not be a problem because the purpose of the molecule is to present the MBP as an "immunogen" while any reacted IgE loaded mast cells would be suppressed by the IgG Fc portion.

In response, the examiner cited McDevitt et al (Proc Natl Acad Sci USA 101(2): 14627-14630, Oct 2004; PTO 892 mailed 6/20/05) for teaching administering autoantigen comprising any "portion" of an autoantigen such as epitopes 206-220, 221-235 and 286-300 of GAD to NOD mice resulted in the prompt onset of an immediate hypersensitivity and *death* of animal (page 14628, col. 2, last paragraph, in particular). In other words, the specific portion of the autoantigen capable of binding to a third polypeptide sequence in the claimed fusion protein is required.

Blanas *et al* (of record, Science 274: 1707-1709, Dec 1996; PTO 1449) teach treating autoimmune rheumatoid arthritis and multiple sclerosis by oral administering autoantigen could lead to onset of autoimmune diabetes (see abstract, in particular). A pharmaceutical composition for treating any autoimmune diseases such as multiple sclerosis in the absence of in vivo working example is unpredictable. Let alone the claimed pharmaceutical composition is for "prevention" of any autoimmune disease.

Couzin *et al*, of record, teach the unpredictability of treating/preventing autoimmune diseases. Couzin et al teach that finding the tell tale antibodies doesn't guarantee that autoimmune diabetes still strike (See page 1863, Science 300: 1862-65, 2003). Couzin *et al* teach that three major prevention trials have failed to stop autoimmune disorder such as type I diabetes (See entire document).

Mackay *et al,* PTO 1449, teach that two recent phase I clinical trial for treatment of multiple sclerosis by administering myelin basic protein peptide resulted in *exacerbations* of multiple sclerosis (See page 346, col. 2, in particular). Further, it is not clear the reliance of a pharmaceutical composition comprising a fusion molecule comprising any IgG heavy chain constant region fused to any sequence at least 90% sequence identity to any portion of the amino

acid sequence of myelin basic protein is appropriate for treating all autoimmune diseases, let alone for "prevention" of any immune diseases in the absence of in vivo working example. The term "prevent" as defined by the Webster's II New Riverside University Dictionary is to keep something from happening, to warding off illness or disease (see page 933, col. 1, in particular). There is not a single in vivo working example in the specification as filed that the claimed pharmaceutical composition could ward off or prevent any autoimmune diseases. There is no indication in the specification as filed that administering any pharmaceutical composition comprising any fusion molecules comprising the altered heavy chain constant region of the IgG fused to any MBP peptide is functional, in vitro or in vivo. Clearly, further experimentation is required. As such, treatment and/or prevention of any immune disease, any immune disease such as any autoimmune disease using any fusion molecule is highly unpredictable, varies depending on the animal model, means of administration and composition of the fusion molecule.

With regard to previously enclosed later published papers which show that fusion molecules comprising an IgG constant region linked to an IgE constant region successfully reduces histamine release in animals, those references do not teach fusion molecules comprise the heavy chain constant region of the IgG fused to the MBP peptide.

7. Claims 1, 4-5, 9-14, 16-34 and 40-44 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The specification does not reasonably provide a **written description** of any and all fusion molecule as set forth in claims 1, 4-5, 9-14, 16-34 and 40-44 for treatment or "prevention" of any autoimmune disease.

The specification discloses only an isolated fusion molecule comprising a first polypeptide wherein the first polypeptide consisting of a hinge-CH2-CH3 of human IgG1 constant region of SEQ ID NO: 2 encoded by SEQ ID NO: 1 fused to a full length myelin basic protein comprising SEQ ID NO: 12 or a myelin basic protein epitope consisting the amino acid sequence of SEQ ID NO: 13, and (2) an isolated fusion molecule the hinge-CH2-CH3 of human IgG1 constant region consisting of SEQ ID NO: 1 fused to a human IgE constant region CH2-CH3-CH4 domains of SEQID NO: 7 for inhibiting IgE mediated release of histamine.

With the exception of the specific fusion molecule mentioned above, there is insufficient written description about the structure associated with function of any and all fusion molecules mentioned above without the amino acid sequence. Further, there is inadequate written description about the structure of the first polypeptide in the fusion protein "comprising at least 85% identity" with which IgG heavy chain constant region. The term "comprises" is open-ended. It expands the IgG heavy chain constant region to include the CH1 domain or the whole IgG. In addition, the term "at least 85% identity" means there is at least 15% difference. Not only the length of the first polypeptide is not adequately described, there is inadequate written description about which amino acids within the undisclosed constant region of IgG to be substituted, deleted, added and/or combination thereof such that the first polypeptide of the fusion molecule still binds to the native IgG inhibitory receptor. The same reasoning apply to the first polypeptide as set forth in claim 18-21. Likewise, term "comprises" in claims 22-24 expands the first polypeptide sequence (immunoglobulin Fc region) in the fusion molecule to include additional amino acids at either or both ends in addition to part of the CH2, CH3 and hinge region to include CH1 fragment.

With regard to the second polypeptide of the claimed isolated fusion molecule, the same reasons apply. There is insufficient written description about the "portion" of the amino acid sequence of myelin basic protein (MBP) that is part of the fusion molecule without the amino acid sequence. Further, the term "comprising" is open-ended. There is inadequate disclosure about which amino acids within the portion to be added, deleted, substituted and combination thereof such that the autoantigen comprising at least 10% difference still be able to bind to any native "IgE receptor" through which third polypeptide sequence, especially the third polypeptide is any immunoglobulin instead of IgE class antibody.

With regard to claim 9, there is inadequate written description about the "portion" of myelin basic protein without the amino acid sequence. Further, the term "comprises" is open-ended. It expands the undisclosed "portion" of the myelin basic protein to include additional amino acids at either or both ends. There is insufficient disclosure about which amino acids to be added, much less for the function of the said portion in the claimed fusion protein.

With regard to claim 10, even the autoantigen sequence in the fusion protein comprises the amino acid sequence of SEQ ID NO: 13, SEQ ID NO: 13 is a fragment or an epitope of myelin basic protein. Again, the term "comprises" is open-ended. It expands SEQ ID NO: 13 to

include additional amino acids at either or both ends. There is insufficient disclosure about which amino acids to be added to the autoantigen in the fusion protein.

With regard to claims 18-21, in addition to the problem with the second polypeptide mentioned above, the term "at least 85%, 90%, 95%, 98% identity" to SEQ ID NO: 3 means there is at least 15%, 10%, 5%, 2% sequence difference to SEQ ID NO: 3 in the claimed fusion protein. There is inadequate written description about which amino acids within SEQ ID NO: 3 of the first polypeptide in the claimed fusion protein should or should not be change.

With regard to claims 22-24, in addition to the problem with the second polypeptide mentioned above, the term "comprises" expands the CH2-CH3 domains of a human IgG1 constant region to include the hinge, the CH1 domain or the Fab fragment in the claimed fusion protein. None of the fusion protein in the specification as filed includes CH1 domain or the Fab domain.

With regard to claim 25, in addition to the problem with the second polypeptide mentioned above, there is also inadequate written description about the nucleic acid sequence that "hybridizes" to which "portion" of the complement of the IgG heavy chain constant region of SEQ ID NO: 1, and under which "stringent hybridization conditions". The nucleic acid that hybridizes to the complement of SEQ ID NO: 1 could be any oligonucleotide, which does not encodes the whole IgG heavy chain constant region or the specific Fc domain, let alone encoding a polypeptide in the fusion protein that binds to a native IgG inhibitory receptor. Thus the structure of the oligonucleotide that encodes which portion of the complement of IgG heavy chain constant region that binds native IgG native receptor in the claimed fusion molecule is not adequately described. Further, claim 25 as written is improper for an isolated fusion molecule.

Adequate written description requires more than a mere statement that it is part of the invention. The amino acid sequence itself for the fusion molecule is required. Until the amino acid sequences of the first, and second polypeptides in the fusion protein have been described, the fusion molecule comprising the first and second polypeptide is not adequately described. Since the fusion molecule is not adequately described, it follows that any pharmaceutical composition and article of manufacture comprising any undisclosed fusion molecules are not adequately described.

Finally, the specification discloses only three fusion molecules wherein the fusion molecule comprises a hinge-CH2-CH3 from only human IgG1 constant region consisting of SEQ ID NO: 2 fused to only myelin basic protein comprising SEQ ID NO: 12 (full length) or a peptide

from myelin basic protein consisting of SEQ ID NO: 13, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species of fusion molecule to describe the genus of fusion molecule for the claimed method. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398; University of Rochester v. G.D. Searle & Co., 69 USPQ2d 1886 (CA FC2004).*

Applicant is directed to the Final Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Applicants' arguments filed 12/20/05 have been fully considered but are not found persuasive.

At page 21-23 of the amendment, Applicants' position is that the specification the specification describes the construction of chimeric fusion molecules, see Example 2, pages 80-83. The specification also describes fusion molecules where the first and second polypeptide sequences of the fusion molecule are connected by use of linkers (see Specification page 27, lines 4-15). Also, the fusion molecules may contain post translational modifications, either naturally occurring pr artificial, for example, acetylation, glycosylation or prenylation (as described in the Specification at page 21, line 4 - 24). The Specification describes advantageous fusion molecule variants (page 21, line 25 - page 23, line 3), where the variants have improved affinity for their respective IgG or IgE receptors (Specification, page 34, line 24 - page 35, line 25). The specification describes fusion molecules comprising multiple copies of IgG and autoantigen (page 54, lines 18-21). Fusion polypeptides further comprising signal sequences for intracellular localization or extracellular export (page 63, lines 20-22), and peptide sequence tags to facilitate fusion molecule purification the fusion molecules (page 63, line 32 to page 64, line 3) are also described. With regard to description for polypeptides having at least 85% sequence identity with the IgG constant domain sequences (e.g., 85% sequence identity with SEQ ID NO: 3) where the molecules retain biological activity, the specification describes methods for the determination of percent identity between two amino acid sequences (see Specification, page 23, lines 4 - 13). Also, the Specification provides examples of prior art that describes numerous Ig Fc polypeptides having at least 85% sequence identity with the Fc sequences of SEQ ID NO: 3 (see, the Specification at page 26, line 19 to page 27, line 6). The Specification also describes methods for the identification of Ig Fc sequences having at least 85% sequence identity with the constant domain sequences of SEQ ID NO: 3 (see the Specification at page 23, line 16 to page 24, line 12).

Alternatively still, one of ordinary skill in the art can readily engineer novel Fc domains having at least 85% sequence identity with the constant domain sequences of SEQ ID NO: 3 using recombinant DNA protein engineering techniques.

With respect to the second polypeptide, the sequence for MBP was known in the art prior to Applicant's filing. Applicant provides a number of references in the specification at page 46 which provide the sequence for MBP, see for example, Warren et al., Proc. Natl. Acad. Sci. USA 92:1 1061-65 (1995). The specification identifies the MBP epitope necessary for binding with the autoantibody as MBP83-99. Clearly Applicant had possession of the invention at the time of filing. Applicant points out that all pending claims reciting polypeptides having at least 85% sequence identity with IgG Fc domains (e.g., having 85% sequence identity with SEQ ID NOS: 3) contain the functional limitation that the polypeptides also have the ability to bind to the IgG cell surface receptor. The Specification provides description of this limitation where the amino acids necessary for receptor binding and biological activity (page 35, lines 1-25) and methods to determine the affinity of an Fc domain for its cognate receptor (see, for example, page 55, lines 15 - 25) are described. Applicant argues that the specification provides adequate written description for fusion molecules comprising polypeptides having at least 85% sequence identity with IgG constant domain sequences (e.g., 85% sequence identity with SEQ ID NO: 3), especially in view of the state of the prior art, and the high level of skill in the art. Applicant further argues that the scope of the claims finds written description throughout the Specification, and are allowable.

In response, the claims are drawn to any isolate fusion molecule comprising any first polypeptide comprising at least 85% identity to any IgG heavy chain constant region connected directly or indirectly via a polypeptide linker to any second polypeptide autoantigen sequence which comprises at least 90% sequence identity to any portion of the amino acid sequence of myelin basic protein (MBP) that are capable of cross-linking any native IgG inhibitory receptor and any native IgE receptor for treating and prevention of any immune disease, any immune disease such as any autoimmune disease.

The term "portion" as defined in the specification at page 29 is any portion of a polypeptide may range in size from two amino acid residues to the entire amino acid sequence minus one amino acid. The term "at least a portion" encompasses portions as well as the whole of the composition of matter.

The specification discloses only an isolated fusion molecule comprising a first polypeptide wherein the first polypeptide consisting of a hinge-CH2-CH3 of human IgG1 constant region of SEQ ID NO: 2 encoded by SEQ ID NO: 1 fused to a full length myelin basic protein comprising SEQ ID NO: 12 or a myelin basic protein epitope consisting the amino acid sequence of SEQ ID NO: 13, and (2) an isolated fusion molecule the hinge-CH2-CH3 of human IgG1 constant region consisting of SEQ ID NO: 1 fused to a human IgE constant region CH2-CH3-CH4 domains of SEQID NO: 7 for inhibiting IgE mediated release of histamine.

With the exception of the specific fusion molecule mentioned above, there is insufficient written description about the structure associated with function of any and all fusion molecules mentioned above because the amino acid sequence of the fusion molecule is required. There is inadequate written description about the structure of the first polypeptide in the fusion molecule "comprising at least 85% identity" with which IgG heavy chain constant region because the term "comprises" is open-ended. It expands the IgG heavy chain constant region to include the CH1 domain or the whole IgG. In addition, the term "at least 85% identity" means there is at least 15% difference. Not only the length of the first polypeptide is not adequately described, there is inadequate written description about which amino acids within the undisclosed constant region of IgG to be substituted, deleted, added and/or combination thereof such that the first polypeptide still binds to the native IgG inhibitory receptor in the fusion molecule. Further, there is insufficient written description about the "portion" of the amino acid sequence of myelin basic protein (MBP) that is part of the fusion molecule without the amino acid sequence. Again, the term "comprising" is open-ended. It expands the undisclosed portion of MBP to include additional amino acids at either or both ends. There is inadequate disclosure about which amino acids within the portion to be added, deleted, substituted and combination thereof such that the autoantigen comprising at least 10% difference still be able to bind to any native "IgE receptor" through which third polypeptide sequence, especially the third polypeptide is any immunoglobulin instead of IgE class antibody.

With regard to the argument that the specification describes methods for the determination of percent identity between two amino acid sequences (see Specification, page 23, lines 4-13), the specification merely extends an invitation to one of ordinary skill in the art to find any first polypeptide using any known assay method such as RIAs and ELISAs.

With regard to the second polypeptide autoantigen in the fusion molecule, there is inadequate written description about autoantigen sequence which comprises at least 90%

sequence identity to any "portion" of the amino acid sequence of myelin basic protein (MBP). The particular portion such as MBP83-99 or the full-length sequence of MBP fused to IgG heavy chain constant region is not recited in claim 1. Not only the "portion" of MBP in the fusion molecule is not adequately described, the term "comprises" is open-ended. It expands the undisclosed portion to include additional amino acids at either or both ends. There is insufficient disclosure about which amino acids to be added, much less for the function of the said portion. Finally, the term "at least 90% sequence identity" means there is at least 10% difference. There is inadequate written description about structure of the second polypeptide in the fusion protein that has at least 10% difference compared to the autoantigen MBP.

The specification discloses only three fusion molecules wherein the fusion molecule comprises a hinge-CH2-CH3 from only human IgG1 constant region consisting of SEQ ID NO: 2 fused to only myelin basic protein comprising SEQ ID NO: 12 (full length) or a peptide from myelin basic protein consisting of SEQ ID NO: 13, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species of fusion molecule to describe the genus of fusion molecule for the claimed method. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398; University of Rochester v. G.D. Searle & Co., 69 USPQ2d 1886 (CA FC2004).*

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

9. Claims 1, 4-5, 9-14, 16-34 and 40-44 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The "through a third polypeptide ...receptor" in claim 1 is indefinite and ambiguous because it is not clear whether the "third polypeptide" is part of the fusion molecule. One of ordinary skill in the art cannot appraise the metes and bound of the claimed invention.

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 103(a) that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person

having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

11. This application currently names joint inventors. In considering Patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

12. Claim 1, 4-5, 9-14, 16, 22-28, and 40-41 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Pat No. 5,116,964 (May 1992; PTO 892) in view of US Pat No 5,858,980 (Jan 1999; PTO 892).

The '964 patent teaches an isolated fusion molecule comprising a first polypeptide such as the constant domain of the IgG heavy chain or the Fc portion of human IgG1, IgG2, IgG3, IgG4 which obviously capable of binding to its native IgG inhibitory receptor such as FcγRIIb IgG receptor fused to a second polypeptide autoantigen sequence such as myelin-associated glycoprotein (MAG) or a portion thereof (see abstract, col. 1, line 34, col. 7, line 45, col. 10, lines 10-15, col. 14, lines 65-67, col. 15, lines 4-17, claims 5 and 7, in particular). The reference full-length autoantigen myelin-associated glycoprotein (MAG) comprises at least one autoantigenic epitope. The reference autoantigen myelin-associated glycoprotein (MAG) in the reference fusion molecule obviously is capable of binding to IgE autoantibodies that are specific for myelin-associated glycoprotein (MAG) when administered to a human subject, in turn, the myelin-associated glycoprotein (MAG) specific IgE autoantibodies are capable of binding to its native IgE receptors such as FcεRI IgE receptor and FcεRII IgE receptor. The '964 patent teaches the fusion protein wherein the Fc constant retain at least functionally active hinge, CH2, and CH3 domains of an immunoglobulin heavy chain (see col. 10, lines 10-25, in particular). The reference IgG heavy chain constant region in the fusion molecule has at least 98% sequence identity to the claimed human IgG Fc of SEQ ID NO: 2 (see reference SEQ ID NO: 7, in particular). The advantage of Fc improves the in vivo plasma half-life of the fusion molecule (see col. 15, lines 19-20, in particular). The '964 patent teaches a pharmaceutical composition comprising the reference fusion molecule and pharmaceutical acceptable ingredient such as

calcium non-phosphate buffer and/or cofactor (see col. 31, lines 4-10, in particular). The '964 patent further teaches the fusion molecule wherein the first and second polypeptide are functionally connected through a polypeptide linkers such lysine residues, as well as other amino, amino, carboxyl, sulfhydryl, hydroxyl or other hydrophilic groups (see col. 23, lines 40-44, in particular). The '964 patent further teaches the reference fusion molecule includes a signal sequence at the N-terminus of hybrid molecule (see col. 26, lines 24-29, in particular), and a secretory leader recognized by the host cells (see col. 26, lines 32-56, in particular). Claim 25 is included in this rejection because the recitation of nucleic acid hybridizing under stringent conditions to at least a portion of the complement of the IgG heavy chain constant region of claimed human IgG Fc of SEQ ID NO: 1 would obviously include the reference human IgG Fc.

The claimed invention as recited in claim 1 differs from the teachings of the reference only in that the fusion molecule wherein the autoantigen sequence is at least 90% identity to at least a portion of the amino acid sequence of myelin basic protein (MBP) instead of myelin-associated glycoprotein (MAG).

The claimed invention as recited in claim 9 differs from the teachings of the reference only in that the fusion molecule wherein the autoantigen sequence present in the fusion molecule comprises at least a portion of the amino acid sequence of myelin basic protein instead of myelin-associated glycoprotein (MAG).

The '980 patent teaches autoantigen such as human myelin basic protein (MBP) and various fragments of MBP such as SEQ ID NO: 18-23, and 16 (see claims of '980 patent, in particular). The reference MBP peptide ENPVVHFFKNIVTPRTP of SEQ ID NO: 18 is 100% identical to the claimed peptide of SEQ ID NO: 13. The '980 patent teaches a pharmaceutical composition comprising protein incorporating immuno dominant epitopes of the reference peptides and pharmaceutical acceptable carrier for administration to patients suffering from multiple sclerosis (see col. 3, lines 45-67, col. 11, lines 20-35 in particular).

Therefore, it would be been obvious to one having ordinary skill in the art at the time the invention was made to substitute the myelin-associated glycoprotein (MAG) in the IgG heavy chain constant fusion molecule as taught by the '964 patent for the myelin basic protein (MBP) that is 100% identical to at least a portion of the amino acid sequence of myelin basic protein (MBP) as taught by the '980 patent. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art at the time the invention was made would have been motivated to do this because the Fc improves the in vivo plasma half-life of the fusion molecule as taught by the' 964 patent (see col. 15, lines 19-20, in particular). The '980 patent teaches protein incorporating immuno dominant epitopes of the reference peptides is useful as a pharmaceutical composition for treating patients suffering from multiple sclerosis (see col. 3, lines 45-67, col. 11, lines 20-35 in particular). Claim 28 is included in this rejection because it is within the purview of one ordinary skill in the molecular biology art to use any linker sequence consists of about 5 to about 25 amino acid residues without undue experimentation.

13. Claims 18-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Pat No. 5,116,964 (May 1992; PTO 892) in view of US Pat No 5,858,980 (Jan 1999; PTO 892) as applied to claims 1, 4-5, 9-14, 16, 22-28, and 40-41 mentioned above and further in view of US Pat No 5,565,335 (of record, Oct 1996; PTO 892).

The combined teachings of the '964 patent, and the '980 patent have been discussed supra.

The claimed invention in claim 18 differs from the combined teachings of the references only in that the fusion molecule wherein the first polypeptide sequence comprises an amino acid sequence having at least 85% identity to amino acid sequence of SEQ ID NO: 3.

The claimed invention in claim 19 differs from the combined teachings of the references only in that the fusion molecule wherein the first polypeptide sequence comprises an amino acid sequence having at least 90% identity to amino acid sequence of SEQ ID NO: 3.

The claimed invention in claim 20 differs from the combined teachings of the references only in that the fusion molecule wherein the first polypeptide sequence comprises an amino acid sequence having at least 95% identity to amino acid sequence of SEQ ID NO: 3.

The '335 patent teach various fusion molecule comprising IgG heavy chain constant region polypeptide having an amino acid sequence at least 97.2% identical to the claimed SEQ ID NO: 3, which is at least 85%, 90%, and 95% identical to the claimed SEQ ID NO: 3 (See reference SEQ ID NO 7, in particular). The reference IgG heavy chain is fused to a second autoantigen polypeptide such as myelin associated glycoprotein (See col. 4, Detailed description, lines 18-31, in particular). The advantage of the Fc in the fusion molecule enhances the plasma half-life of the fusion molecule (see Summary of invention, col. 5, lines 26-47, Table IV, in particular).

Therefore, it would be been obvious to one having ordinary skill in the art at the time the invention was made to substitute the IgG heavy chain constant region (Fc) polypeptide in the fusion molecule comprising a first polypeptide at least 85% identity with an IgG heavy chain fused to myelin basic protein as taught by the '964 patent, and the '980 patent for the human IgG1 Fc having an amino acid sequence at least 97.2% identical to the claimed SEQ ID NO: 3 as taught by the '335 patent. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art at the time the invention was made would have been motivated to do this because the '335 patent teaches that Fc fusion molecule enhances the plasma half-life of the fusion molecule (see Summary of invention, col. 5, lines 26-47, in particular). The Fc improves the in vivo plasma half-life of the fusion molecule as taught by the '964 patent (see col. 15, lines 19-20, in particular). The '980 patent teaches the immunodominant epitope of myelin basic protein is useful as a pharmaceutical composition for treating patients suffering from multiple sclerosis (see col. 3, lines 45-67, col. 11, lines 20-35 in particular).

14. Claims 29-34 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Pat No. 5,116,964 (May 1992; PTO 892) in view of US Pat No 5,858,980 (Jan 1999; PTO 892) as applied to claims 1, 4-5, 9-14, 16, 22-28, and 40-41 mentioned above and further in view of Elias et al (of record, J Biol Chem 265(26): 15511-17, September 1990; PTO 892) and Marks et al (of record, J Cell Biol 135(2): 341-354, Oct 1996; PTO 892).

The combined teachings of the '964 patent, and the '980 patent have been discussed supra.

The claimed invention in claim 29 differs from the combined teachings of the references only in that the fusion molecule comprises at least one amino terminal ubiquitination target motif.

The claimed invention in claim 30 differs from the combined teachings of the references only in that the fusion molecule comprises at least one proteasome proteolytic signal, wherein said signal is selected from the group consisting of large hydrophobic amino acid residues, basic amino acid residues, and acidic amino acid residues.

The claimed invention in claim 31 differs from the combined teachings of the references only in that the fusion molecule comprises large hydrophobic amino acid residues, basic residues, and acid amino acid residues.

The claimed invention in claim 32 differs from the combined teachings of the references only in that the fusion molecule comprises at least one endopeptidase recognition motif.

The claimed invention in claim 33 differs from the combined teachings of the references only in that the fusion molecule comprises a plurality of endopeptidase recognition motifs.

The claimed invention in claim 34 differs from the combined teachings of the references only in that the fusion molecule comprises at least one endopeptidase recognition motif selected form the group consisting of cysteine amino acid residue.

Elias et al teach N terminal residue of the protein is one important structural determinant recognized by ubiquitin ligase and conjugated protein to ubiquitin targets the protein for protein degradation (See page col. 15511, col. 2, second paragraph, in particular). Elias et al teach protein with hybrophobic amino acid residues such as leucine, or basic amino acid residues such as histidine, arginine and lysine determines the half-life of the protein (See paragraph, bridging page 15511 and 15512, in particular).

Marks et al teach adding ubiquitination target motif such as bulky hydrophobic group di-leucine motif to any protein would target the protein to the lysosome or endosomal compartments for antigen processing to be release from the cell (See abstract, page 348, in particular).

Therefore, it would be been obvious to one having ordinary skill in the art at the time the invention was made to include at least one amino terminal ubiquitination target motif such as large hydrophobic amino acid residue such as leucine as taught by Elias and Marks to the fusion molecule comprising IgG heavy chain constant region fused to a second autoantigen polypeptide of myelin basic protein (MBP) as taught by the '964 patent, and the '980 patent. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art at the time the invention was made would have been motivated to do this because Elias et al teach adding hybrophobic amino acid residues such as leucine, or basic amino acid residues such as histidine, arginine and/or lysine to the amino terminal of any protein modulates the half-life of the protein (See page 1552, col. 1, in particular). Marks et al teach adding ubiquitination target motif such as bulky hydrophobic group di-leucine motif to any protein would target the protein to the lysosome or endosomal compartments for antigen processing to be release from the cell (See abstract, page 348, in particular). It is within the purview of one ordinary skill in the art at the time the invention was made to have more than

one endopeptidase recognition motifs since it is an obvious variation of the reference teachings of Mark et al.

15. Claims 42-44 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Pat No. 5,116,964 (May 1992; PTO 892) in view of US Pat No 5,858,980 (Jan 1999; PTO 892) as applied to claims 1, 4-5, 9-14, 16, 22-28, and 40-41 mentioned above and further in view of US Pat No 5,945,294 (of record, Aug 1999, PTO 892).

The combined teachings of the '964 patent, and the '980 patent have been discussed supra.

The claimed invention in claim 42 differs from the combined teachings of the references only in that an article of manufacture comprising a container, a fusion molecule of claim 1 within the container, and a label or package insert on or associated with the container.

The claimed invention in claim 43 differs from the combined teachings of the references only in that an article of manufacture comprising a container, a fusion molecule of claim 9 within the container, and a label or package insert on or associated with the container.

The claimed invention in claim 44 differs from the combined teachings of the references only in that an article of manufacture comprising a container, a fusion molecule of claim 9 within the container, and a label or package insert on or associated with the container wherein the label or package insert comprises instructions for the treatment of an immune disease.

The '294 patent teaches diagnostic kit, which is an article of manufacture (for IgE detection using human Fc epsilon receptor (See abstract, in particular). The kit is useful for diagnosing abnormal conditions in animals that are associated with changing levels of IgE associated with allergy (See column 15, lines 19-23, in particular). A kit will allow for ease of use for the practitioner since all the necessary reagents, standard and instructions for use are included in a kit as taught by '294 (See column 14, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the human Fc epsilon receptor in a kit as taught by the '294 patent for the fusion molecule comprising IgG heavy chain constant region fused to a second autoantigen polypeptide of myelin basic protein (MBP) as taught by the '964 patent, and the '980 patent for treating autoimmune disease as taught by the '980 patent. One would have been motivated, with a reasonable expectation of success to do this for convenience and commercial expedience. A kit will allow for ease of use for the practitioner since all the necessary reagents,

standard and instructions for use are included in a kit as taught by '294 (See column 14, in particular). From the teaching of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Claim 44 is included in this rejection because a product is a product, irrespective of its intended use.

16. Claims 17 and 21 are free of prior art.

17. No claim is allowed.

18. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phuong Huynh "NEON" whose telephone number is (571) 272-0846. The examiner can normally be reached Monday through Friday from 9:00 am to 5:30 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The IFW official Fax number is (571) 273-8300.

19. Any information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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